

ADVANCES IN STROKE

2025 Neurocritical Care Updates in Cerebrovascular Disease

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The past year yielded a plethora of clinical trials, many of which were published in broad general medical journals and impacting the field of neurocritical care: from endovascular management of subacute-chronic subdural hematomas (SDH)^{1–3} to fever prevention in vascular brain injury,⁴ prevention of cerebral edema,⁵ blood pressure (BP) management and surgical intervention in intracerebral hemorrhage (ICH),⁶ and hemoglobin targets in aneurysmal subarachnoid hemorrhage (SAH) and acute brain injury.^{7,8} There was also a significant development identifying cognitive motor dissociation (CMD) in brain-injured patients with disorders of consciousness with implications for neuroprognostication.⁹ This article is a narrative summary of selected highlights from key neurocritical care literature published in the past year (Figure).

SUBDURAL HEMATOMA: ENDOVASCULAR ADJUNCTS REDUCE RECURRENCE

Subacute and chronic SDHs are increasingly prevalent in aging populations and carry a high risk of recurrence after surgical evacuation, particularly among patients with frailty or those on anticoagulation. From 2024 to 2025, 2 landmark randomized trials in North America and Europe, EMBOLISE (Embolization of the Middle Meningeal Artery With ONYX Liquid Embolic System for Subacute and Chronic Subdural Hematoma) and STEM (Squid Trial for the Embolization of the Middle Meningeal Artery), reported that adjunctive middle meningeal artery embolization (MMAE) reduces recurrence and treatment failure across a range of presentations and treatment strategies.^{1,2} A third trial from

China, MAGIC-MT (Managing Non-Acute Subdural Hematoma Using Liquid Materials: A Chinese Randomized Trial of MMA Treatment), did not demonstrate benefit but was associated with lower serious adverse events.³

Mechanistically, MMAE uses embolic agents (glue and particles) to block the middle meningeal artery from supplying blood to the dura and membrane surrounding the SDH, thus allowing hematoma reabsorption and preventing recurrent bleeding. EMBOLISE, a prospective, multicenter, adaptive-design trial, randomized 400 patients with symptomatic subacute or chronic SDH and an indication for surgical evacuation to surgery±adjunctive MMAE using Onyx. The addition of embolization showed benefits on the primary end point, hematoma recurrence or progression requiring repeat surgery within 90 days, from 11.3% to 4.1% (relative risk, 0.36; $P=0.008$), yielding a number needed to treat of 14. This reduction occurred without additional functional decline (modified Rankin Scale [mRS] score worsening in 11.9% versus 9.8%, noninferior) and despite a nonsignificant higher numerical 90-day mortality in the treatment group (5.1% versus 3.0%). Serious adverse events occurred in 2.0% of patients. EMBOLISE targeted high-risk patients with large hematomas (mean thickness ≈21 mm), midline shift (≈8 mm), and frequent anticoagulant use (≈38%). Embolization was technically successful in 93.9% of cases, with low reflux rates (1.6%) and a complete absence of visual complications. Although the primary outcome was based on surgical retreatment, which may be influenced by clinician behavior, the design included independent adjudication, imaging review, and consistent secondary outcomes. EMBOLISE provides the first class I evidence supporting MMAE as an effective adjunct to

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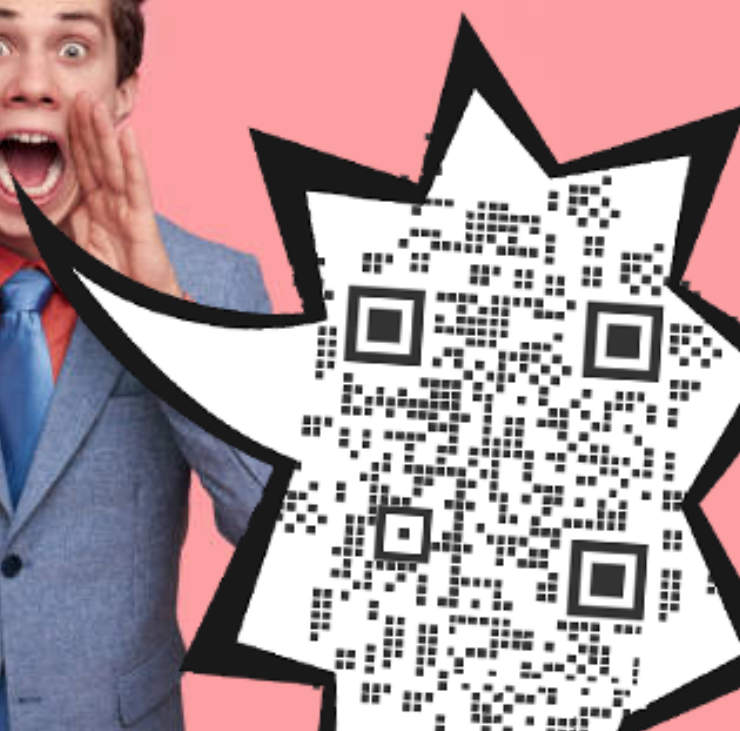
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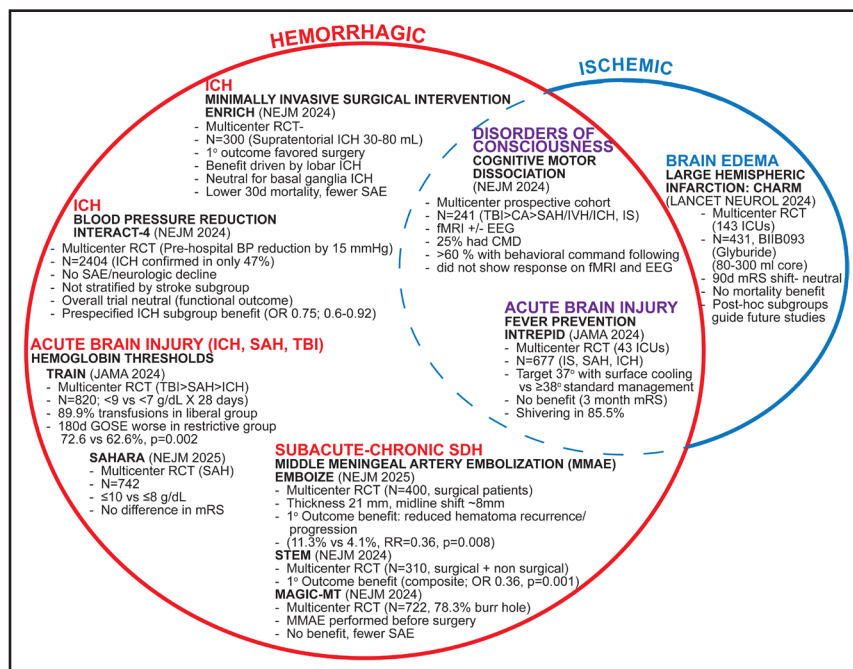


Figure. Summary of studies discussed showing distribution between hemorrhagic vs ischemic disease (as well as those with overlapping and heterogeneous patient populations).

BP indicates blood pressure; CA, cardiac arrest; CMD, cognitive motor dissociation; EEG, electroencephalography; fMRI, functional magnetic resonance imaging; GOSE, Glasgow Outcome Scale-extended; ICH, intracerebral hemorrhage; ICU, intensive care unit; IS, ischemic stroke; IVH, intraventricular hemorrhage; JAMA, *Journal of the American Medical Association*; MMAE, middle meningeal artery embolization; mRS, modified Rankin Scale; NEJM, *The New England Journal of Medicine*; OR, odds ratio; RCT, randomized controlled trial; RR, relative risk; SAE, serious adverse events; SAH, subarachnoid hemorrhage; SDH, subdural hematoma; and TBI, traumatic brain injury.

surgery in reducing the need for reoperation in this population. Conversely, MAGIC-MT, a multicenter, open-label trial, analyzed 722 patients with symptomatic nonacute SDH randomized to MMAE and reported no difference in 90-day incidence of symptomatic recurrence/progression versus usual care but a lower incidence of serious adverse events. Unlike EMBOLISE, patients in MAGIC-MT were assigned to burr-hole drainage versus nonsurgical treatment at the surgeon's discretion, and 78.3% underwent burr-hole drainage. Another key difference is timing: in MAGIC-MT, embolization was performed before surgery in almost all surgical patients versus postoperatively in 42% of patients in EMBOLISE.

STEM extended the role of MMAE beyond surgical patients. In this 310-patient, multicenter trial, embolization using the squid liquid agent was tested as an adjunct to either surgical or nonsurgical standard care. The primary composite end point, residual or recurrent hematoma >10 mm, reoperation, disabling stroke, MI, or neurological death by 180 days, occurred in 16% of the embolization group versus 36% of controls (odds ratio [OR], 0.36 [95% CI, 0.20–0.66]; $P=0.001$). Subgroup analysis suggested the greatest benefit in nonsurgical patients (19% versus 56%, OR, 0.19) although trends favored embolization in surgical patients as well; these post hoc analyses are not powered for interpretation but may inform future studies. The safety profile was reassuring; disabling stroke or death at 30 days occurred in 3% of both groups. While overall 180-day mortality was slightly higher in the embolization group (8% versus 5%), neurological deaths were fewer (1% versus 2%). These data suggest that embolization may shift the treatment paradigm, particularly for patients previously managed conservatively due to surgical risk or hematoma stability.

EMBOLISE and STEM establish MMAE as a valuable tool in SDH management, with benefits in both surgical and nonsurgical contexts. Variation in patient selection (eg, EMBOLISE's inclusion of bilateral SDH versus MAGIC-MT's exclusion of craniotomy patients) may explain differences in efficacy. For instance, EMBOLISE showed a significant reduction in recurrence (4% versus 11%; $P=0.008$), while MAGIC-MT showed a smaller, nonsignificant difference. These differences may stem from patient severity or surgical approach (burr hole versus craniotomy). For neurocritical care teams, this expands the repertoire of minimally invasive interventions capable of reducing recurrence and reintervention in a population prone to frailty, rebleeding, and prolonged recovery. Ongoing studies will refine indications, optimal embolic agents, and the role of MMAE in different timeframes or bilateral cases.

FEVER PREVENTION IN ACUTE VASCULAR BRAIN INJURY: THE INTREPID TRIAL

The impact of fever prevention on recovery post-vascular brain injury is unclear. INTREPID (Impact of Fever Prevention in Brain-Injured Patients) is the largest randomized trial to evaluate this question, enrolling 677 critically ill patients with ischemic stroke, ICH, or SAH across 43 intensive care units.⁴ Patients were randomized to proactive normothermia (target 37.0°C using surface cooling for ≤14 days) or standard fever management initiated at ≥38°C.

The intervention reduced fever burden ($P<0.001$), particularly in ICH and SAH but did not improve outcomes: 3-month median mRS score was 4 in both groups, with

no shift in distribution (OR, 1.09 [95% CI, 0.81–1.46]; $P=0.54$). Good outcome rates (mRS scores, 0–3) were also similar (39.2% versus 42.8%).

The approach was safe but not benign; shivering occurred in 85.5% of patients receiving surface cooling although this caused therapy discontinuation in $\leq 8\%$. Major adverse events and mortality were comparable. Notably, 25% of standard-care patients never developed fever, suggesting limited opportunity for benefit in this mixed population.

INTREPID confirms that proactive temperature control is feasible but should not be routinely used to improve stroke outcomes in the intensive care unit. Reflexive and diffuse/nonselective use of surface cooling devices may be deferred for now based on provider discretion and case-specifics, particularly in resource-limited settings, given the absence of benefit and high incidence of shivering. Future strategies may require physiological or biomarker-based enrichment to target those most likely to benefit.

PREVENTING BRAIN EDEMA IN LARGE HEMISPHERIC INFARCTION: THE CHARM TRIAL

CHARM (Intravenous Glibenclamide for Cerebral Oedema After Large Hemispheric Stroke) was the first phase 3, double-blind, placebo-controlled study of intravenous glibenclamide (BIIB093) for patients with large hemispheric infarction, aiming to reduce cerebral edema and improve functional outcomes.⁵ Across 143 centers, 431 patients aged 18 to 70 years with core infarct volumes of 80 to 300 mL or Alberta Stroke Program Early Computed Tomographic Score of 1 to 5 were randomized within 10 hours of stroke onset. The primary outcome, mRS shift at 90 days, was neutral (common OR, 1.17 [95% CI, 0.80–1.71]; $P=0.42$), and no differences in mortality or midline shift were observed. Results from this trial do not change the current management of cerebral edema after large hemispheric infarction. Post hoc analyses suggested a signal for potential benefit in specific patient subgroups based on infarct volume/endo-vascular treatment. It is important to note that these post hoc data are not powered for clinical interpretation with a high risk of both type-1 and type-2 errors. Nonetheless, the signals may be helpful to guide future trial design.

No new safety concerns emerged beyond manageable hypoglycemia. While CHARM did not support routine use of glibenclamide in unselected patients with large hemispheric infarction, the role of SUR1-TRPM4 (sulfonylurea receptor-1–transient receptor potential cation channel subfamily-M member-4) inhibition as an adjunct in well-defined subgroups, such as those with moderate infarct volume or concurrent reperfusion, remains open. Future trials should consider enriched

designs, volume-based thresholds, and refined imaging to clarify if any patients may benefit.

BLOOD PRESSURE MANAGEMENT IN ICH: THE INTERACT-4 TRIAL

INTERACT-4 (Intensive Ambulance-Delivered Blood Pressure Reduction in Hyper-Acute Stroke Trial-4) tested whether initiating BP reduction in the ambulance, before stroke type is known, improves functional outcomes in suspected acute stroke.⁶ Among 2404 randomized patients, imaging later confirmed ICH in nearly half (47%). While the overall trial was neutral, the prespecified subgroup of patients with ICH showed benefit from prehospital BP reduction (common OR, 0.75 [95% CI, 0.60–0.92]).

Intervention reduced systolic BP by 15 mmHg on average by the time of hospital arrival (159 versus 170 mmHg), with treatment initiated a median of 61 minutes after symptom onset. This ultraearly reduction aligns with prior observational data suggesting rapid hematoma expansion, often within the first 2 hours, which may be mitigated by timely BP control. The intervention appeared safe, with no increase in serious adverse events or early neurological deterioration. This bolsters the rationale for time-sensitive BP lowering in ICH and extends prior hospital-based trials (eg, INTERACT-2 [Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial] and ATACH-2 [Antihypertensive Treatment of Acute Cerebral Hemorrhage-2]) by demonstrating benefits when therapy is initiated acutely in the field. However, because the trial was not stratified by stroke subtype at the time of treatment, the risk-benefit calculus remains complex in real-world settings where ischemic stroke and ICH cannot yet be rapidly distinguished. The results support the development of prehospital triage tools or mobile imaging to enable targeted delivery of early BP management in ICH.

SURGICAL INTERVENTIONS FOR INTRACEREBRAL HEMORRHAGE: THE ENRICH TRIAL

ENRICH (Early Minimally Invasive Removal of Intracerebral Hemorrhage) provides the strongest evidence to date that early, minimally invasive hematoma evacuation may improve outcomes in select patients with ICH.¹⁰ In this randomized, multicenter trial, 300 patients with supratentorial ICH (30–80 mL) were randomized within 24 hours to either transsulcal parafascicular surgery or guideline-based medical management.

The primary outcome, utility-weighted mRS at 180 days, favored surgery (0.458 versus 0.374; posterior probability of superiority, 0.981). Benefit was driven entirely by patients with lobar ICH (mean difference, 0.127); outcomes for anterior basal ganglia

hemorrhages were neutral. Surgical patients also had lower 30-day mortality (9.3% versus 18.0%) and fewer serious adverse events.

Importantly, 73% of surgical patients achieved a postop hematoma volume ≤ 15 mL, and rebleeding rates were low. These results suggest that in carefully selected lobar ICH cases, treated early, minimally invasive evacuation may reduce disability and mortality. ENRICH differentiates itself from prior trials through focused patient selection, early intervention, and procedural standardization.

HEMOGLOBIN THRESHOLDS IN ACUTE BRAIN INJURY: TRAIN AND SAHARA TRIALS

Optimal transfusion thresholds remain unestablished for patients with acute brain injury in neurocritical care units. The potential benefit (increased oxygen delivery and reduced brain-tissue hypoxia after impaired cerebral blood flow/autoregulation) may/may not be offset by the risk of known complications. TRAIN (Transfusion Strategies in Acute Brain Injured Patients), a multicenter trial in a heterogeneous neurocritically ill population, randomized 820 patients to a liberal (hemoglobin < 9 g/dL) versus restrictive (hemoglobin < 7 h/dL) strategy over 28 days.⁸ Majority of patients had traumatic brain injury ($\approx 60\%$), followed by aneurysmal SAH and ICH. Transfusions occurred in 89.9% of patients in the liberal group versus 48.5% in the restrictive group; 180-day unfavorable outcome (Glasgow Outcome Scale-extended score of 1–5) was higher in the restrictive group (72.6% versus 62.6%; $P=0.002$), an effect that was consistent across prespecified subgroups.

Conversely, SAHARA (Aneurysmal Subarachnoid Hemorrhage - Red Blood Cell Transfusion and Outcome), a multicenter trial in aneurysmal SAH, found no difference between liberal versus restrictive transfusion strategies.⁷ Here, 742 patients at 23 centers were randomized to a liberal (≤ 10 g/dL) versus restrictive (≤ 8 g/dL) strategy to investigate the impact on unfavorable primary outcomes (mRS score, 4–6) and found no difference. The restrictive threshold here was higher than the commonly used 7 g/dL, and the mean hemoglobin level over 21 days was > 9 g/dL in the restrictive group and > 11 g/dL in the liberal group. Most preclinical and retrospective data suggest a potential benefit of a liberal transfusion strategy in aneurysmal SAH during clinical vasospasm; this was not evaluated by SAHARA.

For neurocritical care teams, despite the emergence of large clinical trial data, the jury is still out on the optimal transfusion threshold with increasing evidence suggesting the importance of precision medicine where patient selection, timing, and hemoglobin level may be critical.

DISORDERS OF CONSCIOUSNESS

A multicenter study published in *The New England Journal of Medicine* provides the most comprehensive evidence to date that a significant proportion of patients diagnosed as unconscious may retain covert awareness detectable only by advanced neuroimaging and neurophysiological monitoring.⁹ Among 241 patients with disorders of consciousness who lacked observable command-following (coma, vegetative state, or minimally conscious state-minus), 25% demonstrated evidence of CMD using task-based functional magnetic resonance imaging or electroencephalography paradigms.

CMD was most frequently identified in younger individuals, traumatic brain injury, and later in the postinjury course. The study used stringent operational criteria and automated analysis pipelines across 6 international centers. CMD was most commonly detected when both functional magnetic resonance imaging and electroencephalography were used, highlighting the value of multimodal testing. The study was intentionally designed to minimize false-positive results. Among patients with behavioral evidence of command-following, nearly two-thirds did not show consistent responses on neuroimaging, underscoring the methodologic limitations and false-negative potential of these tools.

Early and accurate identification of CMD may inform prognosis, prevent inappropriate withdrawal of life-sustaining treatment, and prompt tailored rehabilitation. Widespread adoption is limited by infrastructure and expertise requirements. The authors emphasize the need for standardization and prospective validation to guide integration into clinical workflows.

For neurocritical care teams, these findings challenge binary coma classifications and call for a more nuanced approach to diagnosing and managing prolonged disorders of consciousness. CMD screening may soon become a cornerstone of prognostic evaluation in specialized centers.

ARTICLE INFORMATION

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